National PBM Drug Monograph

Adefovir Dipivoxil, Hepsera™

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

January 2003

Introduction

Chronic hepatitis B is one of the leading causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma. The diagnosis of chronic hepatitis B virus (HBV) infection is based on serologic findings; specifically, the continued presence of HBV surface antigen (HBsAg), high levels of HBV DNA, and usually the presence of hepatitis B envelope antigen (HBeAg). HBeAg negative chronic hepatitis B, referred to as presumed precore mutant chronic hepatitis B, is common in Southern Europe and Asia.[1-3]

Treatment goals of chronic hepatitis B include sustained suppression of viral replication (characterized by a suppression of HBV DNA levels, the loss of HBeAg, and the development of antibody to HBeAg [anti-HBe]), improvement in liver histology, and preventing progression of liver disease. Long-term treatment is necessary in patients who have not lost HBeAg or seroconverted to anti-HBe. Approved chronic HBV treatments include interferon-alpha, lamivudine, and adefovir dipivoxil. However, interferon-alpha is poorly tolerated and has limited efficacy in many subpopulations. Although lamivudine has improved efficacy compared to interferon-alpha in patients with chronic HBV, lamivudine has developed emerging resistance.[4-9] Adefovir dipivoxil respresents a new therapeutic agent that appears be well tolerated with little evidence of resistance to date.

Pharmacology/Pharmacokinetics[10-12]

Adefovir dipivoxil is an oral prodrug of adefovir, an acyclic nucleotide analogue with activity against hepadnaviruses, retroviruses, and herpes viruses. The active intracellular metabolite of adefovir, adefovir diphosphate, selectively inhibits HBV DNA polymerases (reverse transcriptases) through competitive inhibition and chain-termination of HBV replication.

Orally administered adefovir dipivoxil undergoes rapid enzymatic hydrolysis, yielding adefovir during the absorption process in the gastrointestinal tract. The oral bioavailability of a 10 mg dose of adefovir dipivoxil is 59%; plasma concentrations are unaffected when taken with food. The pharmacokinetics of adefovir dipivoxil after single and multiple oral administrations are similar in patients with chronic hepatitis B and healthy subjects.

Adefovir is primarily eliminated as unchanged drug by tubular secretion and glomerular filtration. The elimination half-life of adefovir is 6 to 7 hours and 12 to 36 hours for adefovir diphosphate, which allows for once daily dosing. The elimination half-life is significantly reduced in patients with moderate and severe renal impairment (CLcr <50 mL/min or patients with end stage renal disease (ESRD) requiring hemodialysis), and dose interval modifications are necessary in these populations. Dose adjustments are not necessary in patients with hepatic impairment.

There appears to be no substantial differences in the pharmacokinetics of adefovir with regards to age, body weight, sex, or race. However, pharmacokinetic data is not available or limited in the pediatric population, pregnant women or geriatric patients.

FDA Approved Indication(s)

Adefovir dipivoxil has been approved for the treatment of chronic hepatitis B in adults who have compensated liver function with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases or histologically active disease. In addition, adefovir dipivoxil is approved for use

in adults who have clinical evidence of lamivudine-resistant hepatitis B with or without compensated liver function.

Current VA National Formulary Status

Currently available and approved products for chronic hepatitis B treatment include interferon-alpha and lamivudine.

Dosage and Administration[11, 12]

The optimal dose of adefovir dipivoxil is 10 mg daily. The dosing interval of adefovir dipivoxil should be adjusted to once every 48 hours in patients with moderate renal impairment (CLcr <50 mL/min) and once every 72 hours in severe renal impairment (CLcr <20 mL/min). In patients with ESRD (CLcr <10 mL/min), adefovir dipivoxil should be administered once weekly following completion of hemodialysis.

Renal functions should be monitored routinely for all patients while on treatment, especially in patients with pre-existing or other risks of renal impairment. The dose of the agent should be adjusted accordingly for renal function.

The optimal duration of treatment is still unknown, and is currently being evaluated in clinical studies.

Adverse Effects (Safety Data)[11, 12]

Pooled adverse effects between adefovir dipivoxil 10 mg are similar to placebo for up to 96 weeks of treatment. The most common adverse events with the use of adefovir dipivoxil include headache, pharyngitis, asthenia, abdominal pain, and flu-like symptoms; these effects occurred in up to 13% of patients. None of these events led to treatment discontinuation.

In chronic hepatitis B patients with adequate renal function, 4% of patients treated with adefovir dipivoxil 10 mg daily had an increase of ≥0.3 mg/dL in serum creatinine from baseline compared to 2% in the placebo group during 48 weeks of treatment. In follow-up of up to 96 weeks, 10% and 2% of patients treated with adefovir dipivoxil had an increase of ≥0.3 mg/dL and ≥0.5 mg/dL from baseline, respectively. Resolution occurred despite continuation of the agent in 69% of cases, 28% remained unchanged, and 5% required discontinuation of the agent. The incidence of nephrotoxicity increases with higher doses, underlying renal dysfunction at baseline, or when there are other risk factors for renal dysfunction during treatment.

Table 1. Adverse Events Reported in Clinical Trials of Adefovir Dipivoxil Compared to Placebo

Adverse Events	Adefovir dipivoxil 10 mg (n = 294)	Placebo (n = 228)
Asthenia	13%	14%
Headache	9%	10%
Abdominal pain	9%	11%
Nausea	5%	8%
Flatulence	4%	4%
Diarrhea	3%	4%
Dyspepsia	3%	2%

Precautions/Contraindications[11]

Although adefovir dipivoxil has limited activity against HIV, administration of the agent in chronic hepatitis B patients with unrecognized or untreated HIV infection may result in emergence of HIV resistance. Thus, patients should be offered HIV antibody testing prior to initiating adefovir dipivoxil.

In patients who do not achieve HBeAg seroconversion, hepatitis may be exacerbated after discontinuation of adefovir dipivoxil. In clinical trials, this occurred in up to 25% of patients resulting in serum alanine aminotransaminase (ALT) elevations (≥10 times the upper limits of normal) and increases in HBV DNA levels but was not associated with hepatic decompensation. Therefore, hepatic functions should be monitored closely after stopping treatment.

Severe lactic acidosis and severe hepatomegaly with steatosis have been reported with the use of nucleoside analogs alone or in combination with antiretrovirals. Most cases have occurred in women and in some cases, have resulted in fatalities. Obesity and prolonged nucleoside analog exposure may be risk factors. Adefovir dipivoxil should be discontinued immediately in any patient that develops clinical signs or laboratory findings suggestive of lactic acidosis or pronounced hepatotoxicity.

The risk of nephrotoxicity may be increased in patients with underlying renal dysfunction and in patients taking concomitant nephrotoxic agents (i.e. cyclosporine, tacrolimus, aminoglycosides, vancomycin, and non-steroidal anti-inflammatory agents). Renal function should be monitored while on treatment and the dose of the adefovir dipivoxil should be adjusted accordingly.

The agent is contraindicated in patients with hypersensitivity to any product component. Adefovir dipivoxil is a pregnancy category C agent and should be used only if benefits outweigh the risks.

Drug Interactions

Adefovir is not a substrate or inhibitor of human cytochrome P450 enzymes. There appears to be no significant drug-drug interactions between concomitant adefovir dipivoxil administration with lamivudine, acetaminophen, or trimethoprim/sulfamethoxazole in healthy volunteers; coadministration with ibuprofen (800 mg three times daily) resulted in 33% higher plasma concentrations of adefovir, which appears related to increased oral bioavailability of adefovir.[11, 13]

There appears to be no drug-drug interactions with concomitant administration of adefovir dipivoxil with ritonavir or nelfinavir. However, adefovir dipivoxil may decrease serum concentrations of delaviridine and saquinavir. Increased plasma concentrations of didanosine occurred with concurrent adefovir dipivoxil administration; this did not correlate with an increased risk of didanosine-related adverse events at adefovir dipivoxil doses of 60 mg or 120 mg daily.[data on file, Gilead Sciences]

Clinical Trials[11, 14-16]

<table>
<tr><td>Citation</td><td>Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med. 2003 Feb 27;348(9):808-16.</td></tr>
<tr><td>Study Goals</td><td>To determine the efficacy and safety of adefovir dipivoxil compared to placebo</td></tr>
<tr><td>Methods</td><td>• Study Design
➢ Phase III multicenter, multinational clinical trial
➢ Randomized (1:1:1)
➢ Double-blinded
➢ Placebo-controlled
➢ Treatment with either adefovir dipivoxil 30 mg daily, adefovir dipivoxil 10 mg daily, or placebo
➢ Primary efficacy endpoint was histological improvement at week 48 of treatment compared to baseline using the Knodell Histologic Activity Index (HAI) score
➢ Secondary efficacy endpoints at week 48 included suppression of HBV replication, biochemical response, HBeAg seroconversion, and safety data
➢ 96 week treatment duration
• Data Analysis
➢ Intention to treat (ITT)
➢ Cochran-Mantel-Haenszel
➢ Two sided significance at alpha=0.05 for pair wise comparisons</td></tr>
<tr><td>Criteria</td><td>• Inclusion criteria
➢ Documented HBsAg positive ≥6 months
➢ HBeAg positive
➢ HBV DNA levels ≥10^6 copies/mL
➢ Elevated ALT (≥1.2 to 10 times the upper limits of normal)
➢ Compensated liver disease
➢ Adequate renal function (serum creatinine ≤1.5 mg/dL)
➢ HIV, HCV, and HDV seronegative
➢ Liver biopsy at baseline

• Exclusion criteria
➢ Previous treatment with interferon or >12 weeks of lamivudine, <6 months prior to enrollment
➢ Treatment with hepatotoxic drugs and nephrotoxic drugs or competitors of renal excretion within 2 month prior to enrollment</td></tr>
<tr><td>Results</td><td>Primary Efficacy Analysis at Week 48
<table>
<tr><th></th><th>N</th><th>Improvement in HAI score[1]</th><th>No Improvement</th><th>Missing/ Unassessable Data</th></tr>
<tr><td>Adefovir dipivoxil 30 mg/day</td><td>165</td><td>59%*</td><td>NA</td><td>NA</td></tr>
<tr><td>Adefovir dipivoxil 10 mg/day</td><td>168</td><td>53%*</td><td>37%</td><td>10%</td></tr>
<tr><td>Placebo</td><td>161</td><td>25%</td><td>67%</td><td>7%</td></tr>
</table>
[1] Defined as ≥2 point decrease in the Knodell necroinflammatory score without concurrent worsening in the Knodell fibrosis score
NA – Not available
*p <0.001 compared to placebo</td></tr>
</table>

Secondary Efficacy Analysis at Week 48

	N	Virologic Response[1]	Biochemical Response[2]	HBeAg Seroconversion[3]
Adefovir dipivoxil 30 mg/day	173	39%[#]	55% (93/169)[#]	14%*
Adefovir dipivoxil 10 mg/day	171	21%[#]	48% (81/168)[#]	12%**
Placebo	167	0%	16% (26/164)	6%

[1] Undetectable serum levels of HBV DNA (<400 copies/mL, Roche Amplicor™ PCR assay)
[2] Normalization of ALT levels
[3] Defined as loss of HBeAg and appearance of anti-HBe

*p<0.05 compared to placebo, **p<0.01 compared to placebo,
[#]p<0.001 compared to placebo

Safety
Adefovir dipivoxil 30 mg daily was associated with the emergence of mild nephrotoxicity in 9% of patients; this did not occur in patients receiving adefovir dipivoxil 10 mg daily or in the placebo group.

Conclusions

Chronic hepatitis B patients treated with adefovir dipivoxil had greater histological improvement and higher virologic, biochemical, and serological response rates compared to placebo. Adefovir dipivoxil 10 mg daily had similar efficacy to 30 mg daily but with less adverse effects and was not associated with nephrotoxicity. There was no evidence of adefovir resistance mutations with up to 48 weeks of treatment.

Critique

Strengths
- Well designed, comprehensive multinational study including Asian, European, and North American sites
- Defined primary and secondary endpoints
- Biopsies were blinded and reviewed by the same histopathologist
- Tested for HBV mutations associated with adefovir resistance

Limitations
- Funded by Gilead Sciences, Inc.
- Enrolled relatively low numbers of African-Americans
- Data on longer term efficacy and safety are pending

Citation

Hadziyannis S, Tassopoulos N, Heathcote J, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. N Engl J Med. 2003 Feb 27;348(9):800-7.

Study Goals

To determine the efficacy and safety of adefovir dipivoxil compared to placebo

Methods

- **Study Design**
  - Phase III multicenter, multinational clinical trial
  - Randomized
  - Double-blinded
  - Placebo-controlled
  - Treatment with adefovir dipivoxil 10 mg daily or placebo
  - Primary efficacy endpoint was histological improvement at week 48 of treatment compared to baseline using the Knodell Histologic Activity Index (HAI) score

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Secondary efficacy endpoints at week 48 included suppression of HBV replication, biochemical response, and safety data
96 week treatment duration

• Data Analysis

Intention to treat (ITT)
Cochran-Mantel-Haenszel
Two sided significance at alpha=0.05 for pair wise comparisons

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<tr><td>Criteria</td><td>
• Inclusion criteria

Documented HBsAg positive ≥6 months
HBeAg negative
Anti-HBe positive
HBV DNA levels $\geq 10^5$ copies/mL
Elevated ALT (≥1.5 to 15 times the upper limits of normal)
Compensated liver disease
Adequate renal function (serum creatinine ≤1.5 mg/dL)
HIV, HCV, and HDV seronegative
Liver biopsy at baseline

• Exclusion criteria

Previous treatment with interferon or >12 weeks of lamivudine, <6 months prior to enrollment
Treatment with hepatotoxic drugs and nephrotoxic drugs or competitors of renal excretion within 2 month prior to enrollment

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<tr><th></th><th>N</th><th>Improvement in HAI Score[1]</th><th>No Improvement</th><th>Missing/ Unassessable Data</th></tr>
<tr><td>Adefovir dipivoxil 10 mg/day</td><td>121</td><td>64%*</td><td>29%</td><td>7%</td></tr>
<tr><td>Placebo</td><td>57</td><td>35%</td><td>63%</td><td>2%</td></tr>
</table>
[1] Defined as ≥2 point decrease in the Knodell necroinflammatory score without concurrent worsening in the Knodell fibrosis score
*p <0.001

Secondary Efficacy Analysis at Week 48
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<tr><th></th><th>N</th><th>Virologic Response[1]</th><th>Biochemical Response[2]</th></tr>
<tr><td>Adefovir dipivoxil 10 mg/day</td><td>123</td><td>51%*</td><td>72%</td></tr>
<tr><td>Placebo</td><td>61</td><td>0%</td><td>29%</td></tr>
</table>
[1] Undetectable serum levels of HBV DNA (<400 copies/mL, Roche Amplicor™ PCR assay)
[2] Normalization of ALT levels
*p<0.001
</td></tr>
<tr><td>Conclusions</td><td>Adefovir dipivoxil 10 mg daily had greater histological improvement, and higher virologic and biochemical response rates compared to placebo in chronic hepatitis B patients who were HBeAg negative. Adefovir dipivoxil was generally well tolerated and side effects were comparable to placebo. There was no evidence of adefovir resistance mutations with up to</td></tr>
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	48 weeks of treatment.
Critique	**Strengths** • Well designed, comprehensive multinational study including Asian, European, and North American sites • Defined primary and secondary endpoints • Biopsies were blinded and reviewed by the same histopathologist • Tested for HBV mutations associated with adefovir resistance **Limitations** • Funded by Gilead Sciences, Inc. • Enrolled relatively low numbers of African-Americans • Longer term efficacy and safety are pending

Citation	**Peters M, Hann HW, Martin P, et al. Adefovir Dipivoxil Alone and in Combination with Lamivudine Suppresses YMDD Mutant Hepatitis B Virus Replication: 48 Week Preliminary Analysis [abstract]. Annual Meeting of the American Association for the Study of Liver Diseases, November 2002.**
Study Goals	To evaluate the safety and efficacy of adefovir dipivoxil alone and in combination with lamivudine compared to continued lamivudine for the treatment of lamivudine-resistant chronic hepatitis B
Methods	• **Study Design** ➢ Multicenter, multinational clinical trial ➢ Randomized (1:1:1) ➢ Double-blinded ➢ Active-controlled ➢ Treatment with adefovir dipivoxil 10 mg monotherapy or in combination with lamivudine 100 mg daily, or lamivudine 100 mg daily ➢ Primary and secondary efficacy endpoint was decrease in HBV DNA compared to baseline at week 16 and week 48 of treatment, respectively ➢ Additional endpoints at week 48 include biochemical response, HBeAg seroconversion, and safety data ➢ 48 week treatment duration • **Data Analysis** ➢ Wilcoxon Rank Sum Test
Criteria	• **Inclusion criteria** ➢ Chronic hepatitis B ➢ HBsAg positive ➢ HBeAg positive ➢ HBV DNA levels $\geq 10^6$ copies/mL ➢ ALT (≥1.2 times the upper limits of normal) ➢ Compensated liver disease ➢ Confirmed HBV YMDD polymerase mutation • **Exclusion criteria** ➢ Not stated

Results

Primary Efficacy Analysis

	N	16 Week Mean Change in Serum HBV DNA log_{10} copies/ml	48 Week Mean Change in Serum HBV DNA log_{10} copies/ml
Adefovir dipivoxil (10 mg/day)	19	-2.45*	-3.06*
Adefovir dipivoxil (10 mg/day) plus Lamivudine (100 mg/day)	20	-2.45*	-2.93*
Lamivudine (100 mg/day)	19	-0.07	-0.05

p<0.001 compared to lamivudine monotherapy

Secondary Efficacy Analysis

	N	Biochemical Response[2]	HBeAg Seroconversion[3]
Adefovir dipivoxil (10 mg/day)	19	47%*	11%
Adefovir dipivoxil (10 mg/day) plus Lamivudine (100 mg/day)	20	53%*	6%
Lamivudine (100 mg/day)	19	5%	0%

[1] Normalization of ALT levels
[2] Defined as loss of HBeAg and appearance of anti-HBe
p<0.005 compared to lamivudine monotherapy

Conclusions

Adefovir dipivoxil 10 mg daily or in combination with lamivudine 100 mg daily resulted in significant reductions in serum HBV DNA, and improved biochemical and serological response rates compared to lamivudine monotherapy in lamivudine-resistant chronic hepatitis B patients. There appears to be no discernable antiviral effect with lamivudine monotherapy in these patients. Patients did not appear to have additional benefit from continued lamivudine use in combination with adefovir dipivoxil.

Critique

Strengths

- Multinational study including European and North American sites
- Used active-control group
- Defined primary and secondary endpoints

Limitations

- Funded by Gilead Sciences, Inc.
- Data in abstract form; preliminary analysis
- Exclusion criteria not specified
- Small sample size
- No African-Americans enrolled
- Longer term efficacy data needed

Acquisition Costs

Generic	trade_name	va_price	valpkg	va_ppu
INTERFERON ALFA-2B,RECOMBINANT 10MILLION UNT/0.2ML INJ,PEN,1.5ML	INTRON A 10MIL UNT/0.2ML INJ PEN 1.5ML	$423.95	1	$423.95
INTERFERON ALFA-2B,RECOMBINANT 10 MILLION UNT/VIL INJ	INTRON A 10 MIL UNT/VIL INJ	$67.48	1	$67.48
INTERFERON ALFA-2B,RECOMBINANT 5MILLION UNT/0.2ML INJ,PEN,1.5ML	INTRON A 5MIL UNT/0.2ML INJ PEN 1.5ML	$220.03	1	$33.74
LAMIVUDINE 100MG TAB	EPIVIR 100MG TAB	$176.82	60	$2.95
ADEFOVIR DIPIVOXIL 10MG TAB	HEPSERA 10MG TAB	$329.35	30	$10.98

Cost Analysis

	Cost per week	Cost per year
Treatment		
Interferon alfa-2b 10 MU, 3 times weekly	$202.44 to $211.98	$10,526.88 to $11,022.70
Interferon alfa-2b 5 MU daily	$236.18	$12,281.36
Lamivudine 100 mg daily	$20.65	$1,078.80
Adefovir dipivoxil 10 mg daily	$76.86	$3,996.72

Conclusions

Adefovir dipivoxil 10 mg daily significantly improved histologic, virologic, biochemical, and serological response rates in HBeAg positive and negative chronic hepatitis B patients compared to placebo. Adefovir dipivoxil appears to have improved efficacy compared to interferon alpha and similar efficacy to lamivudine; however, direct comparative clinical studies are needed. In lamivudine-resistant chronic hepatitis B patients, adefovir dipivoxil reduced viral loads, and improved biochemical and serological response rates compared to lamivudine monotherapy. To date, there appears to be little evidence of adefovir resistance mutations with up to 48 weeks of treatment. Adefovir dipivoxil 10 mg daily appears to be well tolerated, and adverse effects are similar to placebo. The optimal treatment duration still needs to be determined. Long term efficacy and safety data are needed in treatment naïve and lamivudine-resistant patients.

Recommendations

Adefovir dipivoxil has proven efficacy and safety with up to 48 weeks and 96 weeks of treatment in patients with chronic hepatitis B, respectively. Adefovir dipivoxil provides an effective alternative in the treatment of chronic hepatitis B patients who are lamivudine-resistant. Adefovir dipivoxil should have usage criteria developed, which will define specific populations and outcomes for its use.

References:

1. World Health Organization Fact Sheet WHO/204; October 2000.
2. Centers for Disease Control and Prevention (CDC). Summary of Notifiable Diseases, United States 2000. MMWR Morbidity and Mortality Weekly Report 2000;49(53):1-128.
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13. Kearney B, Knight W, Currie G, et al. Drug-drug interaction study between adefovir dipivoxil and lamivudine, paracetamol, ibuprofen, and trimethoprim/sulfamethoxazole [abstract]. Annual Meeting of The European Association for the Study of the Liver, April 2002.
14. Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med. 2003 Feb 27;348(9):808-16.
15. Hadziyannis S, Tassopoulos N, Heathcote J, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. N Engl J Med. 2003 Feb 27;348(9):800-7.
16. Peters M, Hann HW, Martin P, et al. Adefovir dipivoxil alone and in combination with lamivudine suppresses YMDD mutant hepatitis B virus replication: 48 week preliminary analysis [abstract]. Annual Meeting of the American Association for the Study of Liver Diseases, November 2002.

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Date: January 9, 2003

National PBM Drug Monograph Addendum

Adefovir Dipivoxil (Hepsera®)

May 2007

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Please see original monograph at:
http://vaww.pbm.va.gov/drugmonograph/adefovirmonographs.pdf

Introduction[1-2]

High rates of resistance to lamivudine coupled with recent FDA-approval of several anti-HBV agents have led to changes in treatment recommendations for chronic hepatitis B. Currently, adefovir dipivoxil, entecavir, or peginterferon alfa-2a is recommended as first-line therapy for the treatment of chronic hepatitis B in nucleos(t)ide naïve patients. Furthermore, the management of antiviral resistant HBV particularly lamivudine resistant isolates is becoming more frequently encountered in clinical practice.

Current VA National Formulary Alternatives

Current FDA-approved formulary alternatives for treatment of chronic hepatitis B include lamivudine, peginterferon alfa-2a, interferon alfa-2b, adefovir dipivoxil (restricted to GI and ID) and entecavir (restricted to GI and ID).

Efficacy and Safety associated with Long-term Adefovir Therapy

HBeAg-negative chronic hepatitis B[3-5]

This is an extension of the pivotal, Phase III trial (Study 438) utilized to receive the FDA-approved indication for treatment of chronic hepatitis B in HBeAg-negative adults. Refer to original monograph for study design and patient demographics. Briefly, patients with HBeAg-negative chronic hepatitis were randomized to receive adefovir dipivoxil 10mg daily or placebo for 48 weeks (primary efficacy analysis occurred at week 48 for study 438). At week 49, the adefovir dipivoxil treatment arm underwent another randomization to receive either adefovir dipivoxil or placebo for another 47 weeks while the original placebo treatment arm was switched to adefovir dipivoxil. At week 96, 125 of the 139 patients assigned to receive adefovir dipivoxil from weeks 49 to 95 continued in the open-label extension study to evaluate long-term safety and efficacy up to study week 240. In comparison, patients receiving placebo from weeks 49 – 95 were entered in another study although data regarding resistance and hepatocellular carcinoma from these patients were included in these results.

Efficacy endpoints:

- HBV DNA <1000 copies/mL
- Normalization of ALT levels
- HBsAg seroconversion
- Histologic improvement

Of the 125 patients enrolled in the open-label extension trial, 70 patients received adefovir dipivoxil for up to 240 weeks while the remaining 55 patients received study drug up to 192 weeks (these patients received placebo up to week 48). The percent of patients with HBV DNA <1000 copies/mL and normalization of ALT levels decreased over 48 – 240 weeks (Refer to Table 1). However, the authors state that the proportion of patients is similar across the study period when the analysis accounted for patients who dropped out for reasons other than resistance or hepatocellular carcinoma. Five patients underwent HBsAg seroconversion during the study. Long-term adefovir dipivoxil therapy was associated

with histological improvement (Refer to Table 2). Genotypic resistance (A181V, N236T) was detected in 29% of the patients by 240 weeks (Table 3).

Table 1. Efficacy Results (ITT Population)

	48 weeks	96 weeks	144 weeks	192 weeks	240 weeks
HBV DNA <1000 copies/mL	71%	71%	73%	62%	53%
Normalization of ALT levels	75%	65%	68%	63%	59%

Table 2. Histologic Improvement by Ranked Assessment

Response	Patients randomized to adefovir up to 48 weeks (liver biopsy at 48 Weeks; n=112)	Patients in placebo treatment arm, then randomized to adefovir with subsequent open-label adefovir (liver biopsy at 192 weeks; n=22)	Patients in adefovir arm, then randomized to continue adefovir with subsequent open-label adefovir (liver biopsy at 240 weeks; n=24)
Improvement in necroinflammation	80%	86%	83%
Improvement in fibrosis	48%	73%	75%

Table 3. Resistance throughout 240 weeks

	48 weeks	96 weeks	144 weeks	192 weeks	240 weeks
Mutation[a]	0%	3%	11%	18%	29%

[a] Presence of N236T or A181V

Among the 125 patients participating in the open-label extension trial, none of the serious adverse events were considered to be related to study drug. Two patients discontinued adefovir dipivoxil due to adverse events; one patient experienced rise in serum creatinine while the other had an elevation in ALT. Four patients experienced a rise in serum creatinine ≥ 0.5mg/dL from baseline (maximum value = 1.5mg/dL; maximum increase = 0.8mg/dL). There were 6 of the 183 adefovir dipivoxil-treated patients that developed hepatocellular carcinoma during the study period.

In conclusion, this study provides long-term efficacy and safety of adefovir dipivoxil in small cohort of patients with HBeAg-negative chronic hepatitis B. At 5 years, a high percent of patients maintained virologic, biochemical, and histological efficacy; however, adefovir mutations were seen in 29% of patients at year 5. In addition, adefovir dipivoxil was generally well-tolerated during long-term therapy with only two discontinuations related to study drug.

HBeAg-positive chronic hepatitis B[6-8]

This is an extension of the pivotal, Phase III trial (Study 437) utilized to receive the FDA-approved indication for treatment of chronic hepatitis B in HBeAg-positive adults. Limited data are available as only published in abstract. Refer to original monograph for study design and patient demographics. Patients assigned to the adefovir dipivoxil 10mg once daily treatment arm for first 48 weeks were eligible to participate in this open-label extension study to assess long-term safety and efficacy up to 240 weeks if he/she did not seroconvert in years 1 and 2. After completing 48 weeks, the adefovir dipivoxil 10mg once daily arm was randomized to receive adefovir dipivoxil 10mg once daily (n=85) or placebo (n=71). However, there was a "misallocation" of study medication; 91% of patients received at least one incorrect dose of placebo or adefovir dipivoxil in the beginning year 2. At 96 weeks, enrollment for open-label adefovir dipivoxil was available for patients who did not undergo HBeAg seroconversion.

Efficacy endpoints:

- HBeAg seroconversion
- Histologic improvement

Sixty-five patients were included in the extension study. Demographics include median age of 34 years old, 83% male, race (74% Asian, 23% Caucasian), median HBV DNA of 8.45 $\log_{10}$ copies/mL, and median ALT of 2 X ULN. Adefovir dipivoxil therapy was associated with increasing rates of HBeAg seroconversion from 14% to 48% at 48 and 240 weeks, respectively (Refer to Table 4). Improvement in necroinflammation and fibrosis occurred in 67% and 60% of adefovir dipivoxil-treated patients, respectively (Table 5).

Table 4. HBeAg Seroconversion

	48 weeks	96 weeks	144 weeks	240 weeks
HBeAg seroconversion	14%	33%	46%	48%

Table 5. Histologic Improvement by Ranked Assessment

Response	Patients receiving adefovir with liver biopsy at baseline and week 48 (n=150)	Patients receiving adefovir with liver biopsy at baseline and week 240 (n=15)
Improvement in necroinflammation	71%	67%
Improvement in fibrosis	41%	60%

Of the 65 patients enrolled in the extension study, 59% experienced a rebound in HBV DNA or did not achieve suppression of HBV DNA levels by 240 weeks. Genotypic resistance (A181V, N236T) was detected in 20% of patients by 240 weeks.

In respect to safety, adefovir dipivoxil was well-tolerated with no serious adverse events reported. Six patients receiving long-term adefovir dipivoxil had a serum creatinine increase of ≥0.5mg/dL from baseline, which led to the discontinuation of adefovir dipivoxil in 2 of these patients.

In conclusion, this extension study provides efficacy and safety data in a small number of patients receiving adefovir dipivoxil therapy for up to five years; however, the misallocation of study medication from year 1 to 2 limits the internal validity of this study. By year 5, 48% of patients underwent HBeAg seroconversion; however, adefovir resistance was detected in 20% of patients.

Effectiveness of Adefovir dipivoxil in Lamivudine-Refractory Patients

Wait-listed and post-liver transplantation patients[9-10]

This is an open-label, compassionate use study for the treatment of adefovir dipivoxil in lamivudine-resistant chronic hepatitis B in wait-listed and post-liver transplantation patients. The efficacy and safety of administering adefovir dipivoxil was evaluated in this population. Inclusion criteria included 1) detectable serum HBV DNA while receiving lamivudine therapy 2) pre- or post- liver transplantation 3) ALT ≥ 1.2 X ULN 4) PT ≤3 seconds above normal range 5) serum creatinine < 1.5mg/dL 6) serum phosphorus ≥ 2.0mg/dL 7) no history of variceal bleeding or hepatic encephalopathy. Patients were able to receive concurrent administration of hepatitis B immune globulin and/or lamivudine.

Efficacy endpoints:

- Primary:
  - Time-weighted average change in serum HBV DNA ($\log_{10}$ copies/mL) from baseline up to week 24.
- Secondary (Weeks 24, 48, 96, and 144):
  - Change in serum HBV DNA from baseline

- Serum HBV DNA (<1,000 copies/mL)
- HBeAg loss or seroconversion
- Change in ALT from baseline
- Normalization of ALT levels
- Changes in Child-Pugh-Turcotte score compared to baseline
- Normalization of albumin, bilirubin, and prothrombin time

A total of 467 patients were enrolled in the study. All patients were assessed for safety (226 wait-listed and 241 post-transplantation). In comparison, 384 patients (176 wait-listed and 208 post-transplantation) were evaluated for efficacy due to the requirement of baseline and subsequent on-therapy HBV DNA viral load. The wait-listed patients were further sub-grouped to "on-study transplantation" for evaluation of safety (n=61) and efficacy (n=57); these patients were previously part of the wait-listed group and then underwent liver transplantation. Efficacy endpoints for the on-study transplantation were included with the wait-listed patients up to the time the patient underwent liver transplantation. Demographics were reported for wait-listed, post-transplantation, and on-study transplantation. In general, demographics were similar among groups with the following exceptions 1) on-study transplant group had lower serum baseline HBV DNA and serum ALT levels 2) post-transplantation had more patients with lower Child-Turcotte-Pugh scores. Almost all of the patients (462/467) received lamivudine along with adefovir dipivoxil; however, the specific details (e.g., duration of lamivudine therapy) are unknown. The investigators documented lamivudine start date on all patients with stop dates recorded on an unspecified subset.

Efficacy endpoints were evaluated for up to 96 weeks in wait-listed and for up to 144 weeks in post-liver transplantation patients (Refer to Table 6). In the both cohorts, patients experienced improvement in virologic, biochemical and histological response rates. The wait-listed patients experienced an average change in HBV DNA of -3.5 $\log_{10}$ copies/mL at 96 weeks, while the post-liver transplantation patients had a larger reduction in HBV DNA of -4.5 $\log_{10}$ copies/mL at 96 weeks. Both groups had 65% of patients with undetectable HBV DNA levels (<1000 copies/mL) at 96 weeks; this percent increased to 78% in the post-liver transplantation patients at 144 weeks. Normalization of ALT levels was seen in 77% of wait-listed patients at 96 weeks and 58% of post-liver transplantation patients at 144 weeks. Although the number of patients with liver biopsies at baseline and post-therapy were low, improvements in the median Child-Pugh-Turcotte scores were documented in these patients. For the patients that underwent "on-study transplantation", no recurrences of HBsAg or serum HBV DNA have been confirmed (defined as two consecutive positive tests). In addition to adefovir dipivoxil and lamivudine therapy, 34 of the 57 patients received concomitant administration of hepatitis B immune globulin. Longer follow-up is needed in this subpopulation as the median time post-transplant was only 36 months.

Table 6. Efficacy Results

	Wait-Listed[a]			Post-liver transplantation			
	Week 24	Week 48	Week 96	Week 24	Week 48	Week 96	Week 144
Primary Endpoint Time-weighted average change in serum HBV DNA (log_{10} copies/mL) from baseline [Mean (±SD)]	-2.7 (1.3) n=176 p<0.001	_	_	-2.9 (1.3) n=208 p<0.001	_	_	_
Change in serum HBV DNA from baseline (log_{10} copies/mL) [Mean (±SD)]	_	-3.5 (1.6) n=83 p<0.001	-3.5 (1.7) n=22 p<0.001	_	-4.0 (1.6) n=164 p<0.001	-4.5 (1.5) n=96 p<0.001	-4.6 (1.5) n=46 p<0.001
Serum HBV DNA <1,000 copies/mL	_	59% (45/76)	65% (13/20)	_	40% (64/159)	65% (61/94)	78% (35/45)
HBeAg loss	_	48% (15/31)	88% (7/8)	_	31% (30/98)	58% (29/50)	_
HBeAg seroconversion	_	23% (7/31)	38% (3/8)	_	11% (11/98)	34% (17/50)	_
Change in ALT from baseline (IU/L) [Mean (±SD)]	_	-145.2 (227.2) n=75	-103.3 (156.0) N=13	_	-81.1 (156.7) n=137	-72.5 (149.4) n=84	-65.4 (223.4) n=33
Normalization of ALT levels (if >ULN at baseline)	_	77% (49/64)	77% (10/13)	_	51% (56/110)	70% (46/66)	58% (15/26)
Changes in Child-Pugh-Turcotte score from baseline [Median]	_	-2 n=32 p<0.001	-2 n=5 p=0.063	_	-3 n=20 p<0.001	-3 n=11 p=0.001	-3 n=7 p=0.031
Normalization of albumin	_	76% (28/37)	_	_	81% (21/26)	_	_
Normalization of bilirubin	_	60% (28/47)	_	_	76% (29/38)	_	_
Normalization of PT	_	84% (26/31)	_	_	56% (5/9)	_	_

[a] Includes wait-listed patients who never underwent and those who underwent a liver transplantation up to the time of transplantation.

Genotypic analysis was performed on samples with HBV DNA >1000 copies/mL at weeks 48, 96, and 144 to detect adefovir mutations. Adefovir mutation, rtN236T, was only detected in two patients at 96 weeks. (Refer to Table 7). Similarly, resistance mutation (rtN236T) was detected in 2 of 8 patients at week 90 and 128 that experienced virologic rebound (defined as HBV DNA > 1 log_{10} copies/mL from nadir measurement). All four of the patients harboring the rtN236T mutation experienced ALT elevations and virologic rebound.

Table 7. Resistance throughout 144 weeks

	48 weeks (n=96)	96 weeks (n=114)	144 weeks (n=47)
Adefovir resistance	0%	2%	2%

Safety of adefovir dipivoxil was assessed in three populations: on-study transplantation (n=61), wait-listed (n=226), and post-transplantation (n=241). As expected, all post-transplantation patients were receiving nephrotoxic immunosuppressants. High rate of treatment-related adverse events were noted in the post-transplantation (46%) compared to on-study transplantation (15%) and wait-listed (19%). Overall, discontinuation of adefovir dipivoxil secondary to adverse events occurred in 4% of patients, which all appeared to be related to renal adverse events. Approximately half (10/19) of the discontinuations secondary to renal adverse events experienced hepatorenal syndrome or multiorgan failure. Overall, an increase in serum creatinine ($\geq$ 0.5 mg/dL) was detected in 27 (47%) of on-study transplantation, 11 (6%) of wait-listed, and 43 (21%) of post-liver transplant patients. There were 67 deaths reported during the study period; most of the deaths were secondary to complications seen in end-stage liver disease or post liver transplantation. The investigators deemed 3 deaths possibly related to study medication.

In conclusion, adefovir dipivoxil (± lamivudine and/or hepatitis B immune globulin) was shown to be effective and safe in wait-listed or post-transplantation patients with lamivudine-resistant HBV.

Adefovir dipivoxil (± lamivudine) for treatment of lamivudine-resistant chronic hepatitis B[11]
This international, multi-center study randomized patients with lamivudine-resistant chronic hepatitis B to one of the following treatment arms for 48 weeks: 1) adefovir dipivoxil 10mg and placebo once daily 2) lamivudine 100mg and placebo once daily 3) adefovir dipivoxil 10mg and lamivudine 100mg once daily. Inclusion criteria included the following: 1) 16 – 65 years old 2) compensated chronic hepatitis B 3) ALT level = 1.2 - 10 X ULN 4) currently receiving lamivudine therapy for minimum of 6 months 5) YMDD mutant HBV 6) serum HBV DNA level $\geq$6 $\log_{10}$ copies/mL.

Efficacy endpoints:

- Primary:
  - Time-weighted average change in serum HBV DNA ($\log_{10}$ copies/mL) from baseline up to week 16.
- Secondary:
  - Time-weighted average change in serum HBV DNA ($\log_{10}$ copies/mL) from baseline up to week 48.
  - Change in serum HBV DNA from baseline
  - Normalization of ALT levels
  - HBeAg loss
  - HBeAg seroconversion
  - Loss of HBsAg

A total of 59 patients were enrolled in the study. Patient demographics include median age of 45 years old, 79% males, race (60% Caucasian, Asian 36%), 97% HBeAg positive, median HBV DNA of 8.12 $\log_{10}$ copies/mL, and median serum ALT of 79 IU/L.

Compared to the group that received lamivudine monotherapy, the adefovir dipivoxil containing regimens (monotherapy or in combination with lamivudine) demonstrated statistically significant improvement in HBV DNA from baseline to week 16 and week 48 as well as improvement in the secondary virologic and biochemical endpoints (Refer to Table 8).

Table 8. Efficacy Results

	Lamivudine (n=19)		Adefovir[a] (n=19)		Adefovir + lamivudine[a] (n=20)	
	Week 16	Week 48	Week 16	Week 48	Week 16	Week 48
Primary Endpoint Time-weighted avg. change in serum HBV DNA (log_{10} copies/mL) from baseline [Mean (±SD)]	-0.00 (0.34)	-0.10 (0.39)	-2.66 (0.80) p<0.001	-3.38 (1.05) p<0.001	-2.50 (0.54) p<0.001	-3.09 (0.67) p<0.001
Change in serum HBV DNA from baseline (log_{10} copies/mL) [Mean (±SD)]	0.00 (0.28)	-0.31 (0.93)	-3.11 (0.94) p<0.001	-4.00 (1.41) p<0.001	-2.95 (0.64) p<0.001	-3.46 (1.10) P<0.001
Serum HBV DNA <1,000 copies/mL	NR	0%	NR	26% p=0.018	NR	35% p=0.005
HBeAg loss	NR	0%	NR	16% p=0.075	NR	17% p=0.067
HBeAg seroconversion	NR	0%	NR	11% p=0.152	NR	6% p=0.304
Change in ALT from baseline (IU/L) [Mean (±SD)]	NR	0.0 (30.8) 95% CI: -4.2, 14.2	NR	-87.7 (121.7) 95% CI: -143.9,-31.5	NR	-48.6 (82) 95% CI: -84.5, -12.6
Normalization of ALT levels (if >ULN at baseline)	NR	5%	NR	47% p=0.004	NR	53% p=0.001

[a]p-values are compared to lamivudine monotherapy.
NR=not reported

Adverse events were described as "all grades at any time during the study", which led to high percentage of patients experiencing any adverse event (100% in lamivudine arm vs 95% in adefovir dipivoxil vs 90% in adefovir dipivoxil + lamivudine). However, none of the adverse events led to discontinuation of study treatment. Of the 5 serious adverse events reported, the investigators did not consider these related to study medications. Seven patients in the adefovir dipivoxil arm experienced Grade 3 ALT elevations (Table 9), which occurred within 12 weeks of adefovir dipivoxil therapy with the exception of one patient. Five patients had resolution of ALT elevations at week 48 while the remaining two patients experienced reductions in the Grade severity. Of the 3 lamivudine-treated patients with Grade 4 ALT elevations, a reduction occurred to Grade 2 at week 48.

Table 9. Laboratory Abnormalities (maximum postbaseline measurement)

	Lamivudine (n=19)	Adefovir dipivoxil (n=19)	Adefovir dipivoxil + lamivudine (n=20)
ALT elevation Grade 3 Grade 4	 0 (0%) 3 (16%)	 7 (37%) 0 (0%)	 1 (5%) 1 (5%)
AST elevation Grade 3 Grade 4	 1 (5%) 2 (11%)	 1 (5%) 0 (0%)	 0 (0%) 0 (0%)
Amylase Grade 3 Grade 4	 3 (16%) 0 (0%)	 0 (0%) 0 (0%)	 2 (10%) 0 (0%)
Increase in Scr ≥ 0.5mg/dL above baseline	0 (0%)	0 (0%)	0 (0%)
Serum phosphorus level <1.5mg/dL	0 (0%)	0 (0%)	0 (0%)

In conclusion, adefovir dipivoxil monotherapy or in combination with lamivudine demonstrated virologic and biochemical effectiveness in patients with lamivudine-resistant, compensated chronic hepatitis B. The authors noted that more patients in the adefovir dipivoxil monotherapy arm experienced an ALT elevation compared to the combination of adefovir dipivoxil and lamivudine or lamivudine monotherapy arm. These ALT elevations (5-10 times ULN) were not associated with elevations in HBV DNA level or hepatic decompensation. It is hypothesized that adefovir dipivoxil monotherapy may cause a re-emergence of wild-type HBV while adding adefovir dipivoxil to on-going lamivudine therapy may provide protection against this transformation. Due to the potential of ALT flares leading to more severe consequences in patients with advanced stage liver disease (i.e., cirrhosis, decompensated liver disease), combination therapy may be more appropriate for this population.

Adefovir and lamivudine combination therapy compared to adefovir monotherapy in lamivudine resistant patients with HBeAg-negative chronic hepatitis B[12]

This multicenter study conducted in Italy evaluated the long-term efficacy and safety of adefovir and lamivudine combination therapy compared to adefovir monotherapy in lamivudine resistant patients with HBeAg-negative chronic hepatitis B. Limited data are available as only published in abstract. Study design included both retrospective and prospective evaluation of a cohort of 588 patients enrolled in an expanded access program. The efficacy endpoints were the following: 1) HBV-DNA undetectable (<3 $\log_{10}$ copies/mL) 2) virologic breakthrough (>1 $\log_{10}$ HBV DNA) 3) adefovir resistance (presence of mutations and virologic breakthrough) 4) ALT normalization. Safety endpoint was serum creatinine increase >0.5mg/mL from baseline. No statistical significant differences were noted in virological and biochemical responses in the combination versus the monotherapy treatment groups. However, virologic breakthrough [67/273 (24%) vs 13/264 (5%); p<0.001)] and adefovir resistance [29/273 (11%) vs 0/264 (0%); p<0.001)] occurred more frequently in adefovir monotherapy compared to combination therapy. As a result, the combination group maintained higher rate of virological response over 3 years compared to adefovir monotherapy (74% vs 59%, p<0.001). Overall, serum creatinine elevations were noted in 8% of patients; no differences were noted between treatment groups. The authors conclude that adding adefovir to on-going lamivudine therapy rather than switching to adefovir monotherapy may reduce emergence of adefovir mutations.

Adefovir dipivoxil and lamivudine for treatment of lamivudine-resistant chronic hepatitis B in patients with compensated or decompensated liver disease[13]

This study evaluated the efficacy and safety of adding adefovir dipivoxil to on-going lamivudine therapy in patients with chronic hepatitis B harboring the YMDD mutation. Patients were divided into two groups. Group A consisted of patients with compensated, HBeAg-positive hepatitis B; these patients were randomized to receive adefovir dipivoxil 10mg once daily or placebo for 52 weeks along with on-going lamivudine. In comparison, Group B had decompensated or recurrent hepatitis B after liver transplantation; these patients were enrolled in open-label adefovir dipivoxil 10mg once daily for 52 weeks along with on-going lamivudine. Other inclusion criteria included the following: 1) ≥ 18 years old 2) ALT level >1.2 X ULN 3) currently receiving lamivudine therapy for minimum of 6 months 4) YMDD mutant HBV 5) serum HBV DNA level $\geq 10^6$ copies/mL.

Efficacy endpoints:

- Primary:
  - HBV DNA response (defined as percent of patients with HBV DNA $\leq 10^5$ copies/mL or ≥ 2 $\log_{10}$ reduction from baseline at week 48 or 52 if baseline HBV DNA > 10^5 copies/mL).
- Secondary:
  - Assessed for Group A and B
    - Change in serum HBV DNA from baseline
    - Serum HBV DNA (<200 copies/mL)
    - HBeAg loss
    - Normalization of ALT levels
    - Patients with YMDD mutant HBV DNA
  - Assessed only for Group B
    - Histological changes
    - Disease progression (defined as spontaneous bacterial peritonitis, bleeding gastric/esophageal varices or hepatocellular carcinoma during treatment)

A total of 40 patients were enrolled in the study. Patient demographics include median age of 53 years old, 88% males, 68% HBeAg positive, median HBV DNA level of 8.61 $\log_{10}$ copies/mL and mean serum ALT of 127 IU/L.

In Group A, patients who received adefovir dipivoxil with lamivudine had significantly higher HBV DNA response compared to patients that received lamivudine monotherapy. Secondary virologic and biochemical endpoints were also significantly better in the group that received adefovir dipivoxil (Refer to Table 10). In Group B, these non-randomized patients experienced high HBV DNA response rates as well (Table 10). Group B patients who did not receive a liver transplant prior to study entry also experienced an improvement in the median Child-Pugh-Turcotte score of -1.0; however, disease progression occurred in one patient in Group B (variceal hemorrhage).

Table 10. Efficacy Results at week 48 and 52

	Group A[a]		Group B
	Lamivudine + Placebo (n=48)	Lamivudine + Adefovir dipivoxil (n=46)	Lamivudine + Adefovir dipivoxil (n=40)
Primary Endpoint HBV DNA response	5/46 (11%)	39/46 (85%) p≤0.01	36/39 (92%)
Change in serum HBV DNA from baseline (log_{10} copies/mL) [Median]	+0.3	-4.6 p≤0.01	-4.6
Serum HBV DNA <1,000 copies/mL	0/48 (0%)	9/46 (20%) p≤0.01	NR
HBeAg loss	1/42 (2%)	6/40 (15%)	8/27 (30%)
Normalization of ALT levels (if >ULN at baseline)	3/47 (6%)	14/46 (30%) p=0.002	20/38 (53%)
Presence of mutation	44/46 (96%)	26/42 (62%)	21/37 (57%)

[a] p-values are compared to lamivudine monotherapy.

Adverse events (defined as at least one adverse event) were high among patients enrolled in this study. In Group A, adverse events were similar between patients enrolled in lamivudine-placebo arm compared to those in lamivudine-adefovir dipivoxil arm (83% vs 82%). In comparison, Group B patients experienced a higher rate of adverse events (95%). One patient in Group B died secondary to respiratory failure. No serious adverse events were considered to be related to study medications. No elevations of serum creatinine were reported in this study.

In conclusion, chronic hepatitis B patients with lamivudine resistance demonstrated virologic and biochemical improvement with the addition of adefovir dipivoxil to on-going lamivudine therapy. This was seen in patients with compensated or decompensated liver disease.

Safety and efficacy of adefovir dipivoxil in patients infected with lamivudine-resistant hepatitis B and HIV-1[14-17]

This prospective, open-label study evaluated the safety and efficacy of adefovir dipivoxil in patients with lamivudine-resistant hepatitis B and HIV. Adefovir dipivoxil 10mg once daily was added to on-going antiretroviral therapy, which included lamivudine 150mg twice daily. Inclusion criteria included the following: 1) HIV-1 and HBV co-infection 2) currently receiving lamivudine therapy for minimum of 6 months 4) YMDD mutant HBV 5) detectable serum HBV DNA level 6) normal renal function.

Efficacy endpoints:

- Change in serum HBV DNA from baseline
- Change in ALT
- Change in HIV RNA
- Change in $CD4^+$

A total of 35 patients were enrolled in the study. Patient demographics include mean age of 41 years old, 97% males, median serum ALT of 81 IU/L, median HBV DNA of 9.76 $\log_{10}$ copies/mL, mean HIV RNA of 2.89 $\log_{10}$ copies/mL, and mean $CD4^+$ cell count of 422.8 cells/mm^3.

Improvements in virologic and biochemical endpoints for HBV continued throughout the 144 weeks (Table 11). In comparison, HIV RNA levels did not statistically change throughout the 144 weeks while CD4+ count trended upwards (Table 11).

Table 11. Efficacy Endpoints

	48 weeks	96 weeks	144 weeks
Change in serum HBV DNA from baseline [Mean (±SD)]	-4.65 (1.43) P<0.001	-5.63 (1.65) p<0.001	-6.04 (1.88) p<0.001
Change in ALT [Mean (±SD)]	-26.58 (-79.53) 95%CI(-55.75, 2.59)	-43.73 (79.34) 95%CI(-73.36,-14.11)	-49.00 (89.18) 95%CI(-83.81,-14.19)
Change in HIV RNA [Mean (±SD)]	0.21 (0.62) p=0.13	0.04 (0.71) p=0.64	0.05 (0.79) p=0.79
Change in $CD4^+$ [Mean (±SD)]	49.06 (138.06) P=0.111	58.14 (138.28) p=0.034	61.00 (155.46) p=0.05

Genotypic analysis was performed on samples with HBV DNA > 3 $\log_{10}$ copies/mL at weeks 48, 96, and 144 to detect adefovir mutations. Investigators did not detect adefovir mutations (N236T or A181V) in the analyzed samples. Similarly, genotypic analysis was performed on HIV RNA. Four patients were identified to acquire HIV resistance during concomitant adefovir dipivoxil and antiretroviral therapy; however, none of mutations appear to be associated with HIV resistance seen with adefovir dipivoxil.

The addition of adefovir dipivoxil to antiretroviral therapy in patients with co-infection of HIV and HBV was well-tolerated during the 144 week study. Investigators did not deem any of the serious adverse events related to adefovir dipivoxil therapy. An increase in serum creatinine ($\geq$ 0.5 mg/dL) was detected in two patients. Both patients experienced resolution of elevated creatinine, which occurred after discontinuation of study drug in one patient.

In conclusion, the addition of adefovir dipivoxil to patient's on-going antiretroviral therapy (including lamivudine) resulted in statistically significant change in serum HBV DNA from baseline at 48, 96, and 144 weeks ($p<0.001$ for each time period). Adefovir mutations were not detected in HBV DNA or HIV RNA. Significant limitations of this study include the open-label, non-randomized study design, short duration and small sample size. Importantly, adefovir dipivoxil should not be used to treat HBV in a HIV-infected patient who is not receiving antiretroviral therapy. Even though adefovir dipivoxil is not reported to display activity against HIV (at the approved dosage of 10mg once daily), the structural similarities between tenofovir and adefovir raise theoretical concerns that adefovir dipivoxil may select out for HIV mutations. Because tenofovir displays potent in vitro activity against HIV and lamivudine-resistant HBV, many consider tenofovir fumarate as the preferred nucleotide analog to administer in co-infected HIV and HBV patients on antiretroviral therapy. Of note, tenofovir fumarate is currently not FDA-approved for treatment of chronic hepatitis B and still undergoing Phase III trials.

Acquisition Costs
The VA cost of adefovir dipivoxil (one bottle of 30 tablets) is $332.70

Table 12. Cost for anti-HBV agents

Drug	Dose	Cost Dose ($)	Cost/Year/patient ($)
Telbivudine	600mg orally once daily	$11.33	$4135.45
Lamivudine	100mg orally once daily	$4.07	$1485.55
Adefovir dipivoxil	10mg orally once daily	$11.09	$4047.85
Entecavir	0.5mg orally once daily	$14.45	$5274.25
Peginterferon alfa-2a	180mcg subcutaneous once weekly	$126.16	$6560.32
Interferon alfa-2a	10 million IU SQ or IM three times a week	$34.00	$5304.00

Conclusions[1-3, 6, 15-17]
Adefovir dipivoxil is considered a first-line treatment option for chronic hepatitis B in nucleos(t)ide-naïve and in lamivudine-resistant patients. Long-term studies with adefovir-treated patients have shown sustained virologic, biochemical and histological responses over 4 to 5 years in those who did not develop adefovir-resistance mutations. Although lower than lamivudine, adefovir resistance rates have been reported up to 20-29% at 5 years; clinical failure with adefovir has been associated in patients harboring the rtN236T or A181V mutation. Due to adefovir's activity against lamivudine-resistant HBV, adefovir dipivoxil has a major role in the treatment of lamivudine experienced patients. Adefovir dipivoxil may either be added to on-going lamivudine therapy or switched from lamivudine to adefovir dipivoxil in patients with lamivudine-resistant HBV. Experts suggest that combination of lamivudine and adefovir dipivoxil may be preferred therapy for lamivudine-resistant patients with advanced liver disease to reduce the potential development of adefovir resistance. Similarly, adefovir dipivoxil with or without lamivudine is also recommended for the treatment for entecavir- or telbivudine-resistant HBV. Because tenofovir fumarate displays potent activity against HBV and HIV, tenofovir fumarate rather than adefovir dipivoxil is often utilized in patients co-infected with hepatitis B and HIV on antiretroviral therapy. Tenofovir fumarate is currently not FDA-approved for treatment of chronic hepatitis B; however, Phase III comparative trials of tenofovir fumarate and adefovir dipivoxil are on-going. Treatment recommendations for the chronic hepatitis B will continue to evolve over the next several years with the potential FDA-approval of other anti-HBV agents, completion of head-to-head trials of newer anti-HBV agents and further evaluation of the role of combination therapy.

Recommendations
Adefovir dipivoxil is currently utilized as a first-line agent for the treatment of chronic hepatitis B in nucleos(t)ide-naïve patients as well as management of antiviral resistant HBV. Adefovir dipivoxil does not appear to display cross-resistance to lamivudine-, entecavir, or telbivudine-resistant HBV. Similar to other oral nucleos(t)ide agents, long-term adefovir dipivoxil therapy was also associated with increasing resistance over time. Future studies are needed to define the role of combination therapy for the treatment of chronic hepatitis B; this may reduce the incidence of resistance seen with the oral agents.

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